UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606** Master Case No. 15-2606 (RBK/JS) Hon. Robert B. Kugler, U.S.D.J. Hon. Joel Schneider, U.S.M.J.
THIS DOCUMENT RELATES TO ALL CASES	

DEFENDANTS' BRIEF IN SUPPORT OF MOTION TO EXCLUDE TESTIMONY OF DR. DAVID KESSLER

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PRELIMINARY STATEMENT

The issue before the Court is general causation: Do olmesartan-containing medications cause sprue-like enteropathy? Plaintiffs' expert Dr. David Kessler offers three opinions that are irrelevant to this issue: (1) whether there is a causal *association* between olmesartan-containing medications and sprue-like enteropathy under the federal regulatory *labeling* standard; (2) when defendants should have known of that association and revised the warning label on its olmesartan-containing products; and (3) defendants' conduct in responding to causal association evidence. Opinions two and three have nothing to do with general causation—— and therefore challenges to those opinions will be made at a later date if the case survives the *Daubert* challenges.

To the extent Plaintiffs attempt to use Dr. Kessler's "causal association" opinion—pertinent to label changes—to establish scientifically-based general causation, their approach cannot survive a *Daubert* challenge for two reasons. First, Courts have consistently rejected attempts to use the lower regulatory causal association standard as proof of general causation; the lower standard pertinent to labeling changes is not the correct standard to assess scientific causation questions and is thus irrelevant to a general causation inquiry. Second, Dr. Kessler's causal association opinion—even if permitted—is not derived from a reliable, scientific methodology. As established below, he ignores a double-blind randomized

controlled trial—the "gold standard" of causation evidence—that found no association between olmesartan and sprue-like enteropathy, as well as three observational epidemiological studies reaching the same result. He relies instead on anecdotal, uncontrolled case reports, the lowest form of evidence. When epidemiology exists, "it cannot be ignored." *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005). And his case report "analysis" is unreliable because it is subjective, skewed toward a predetermined result, and almost entirely based on the "say-so" of another of plaintiffs' experts, Dr. Daniel Leffler —whose opinion itself is untethered to any objective criteria establishing that the case reports show what Plaintiffs term "olmesartan-associated enteropathy."

In short, because Dr. Kessler's regulatory causation association opinion does not "fit" the general causation inquiry before the Court, it should be excluded from any such analysis. Even if it were germane to the issue at hand it should be excluded because it is not the product of a reliable methodology. Fed. R. Evid. 702; *Daubert v. Merrell Dow Pharms., Inc.* 409 U.S. 579 (1993).

STATEMENT OF FACTS

The Defendants incorporate by reference the General Statement of Facts as set forth in the *Daubert* challenge to Dr. Hutfless.

LEGAL ARGUMENT

I. DR. KESSLER'S REGULATORY CAUSAL ASSOCIATION OPINION DOES NOT ESTABLISH GENERAL CAUSATION.

Dr. Kessler's opinion—that there is reasonable evidence of a causal association between olmesartan and sprue-like enteropathy under the FDA *labeling* standard—does not establish general causation. It is well-established that proof of a causal association is not proof of general causation. *In re TMI Litig.*, 193 F.3d 613, 710 n.159 (3d Cir. 1999) ("Association does not necessarily imply a causal relationship."). It is, rather, "the duty of scientists to rigorously analyze the data to determine whether an association is causal." *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1175 (E.D. Wash. 2009). Dr. Kessler did not take this next step – he stopped at "association" and never did the "rigorous analysis" to determine whether any claimed associations were in fact causal. *See* Certification of Daniel B. Carroll ("Carroll Cert."), Exhibit A, Report of David Kessler, M.D. ("Kessler Rep.") at ¶¶ 2-6; Carroll Cert., Exhibit B, Deposition of David Kessler, M.D. ("Kessler Dep.") at 150:15-18 ("I'm telling you the standard that I used in this report was reasonable evidence, right, of a causal association.").

Dr. Kessler also expressly ties his opinion to a regulatory labeling standard that by its own terms distinguishes casual association from a definitive causal relationship: "[L]abeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association

with [the] drug; a causal relationship need not have been definitively established." 21 C.F.R. § 201.57(c)(6)(i). Dr. Kessler admitted that this regulation sets a lower bar than that required to establish general causation and confined his opinion to this lower standard. *See, e.g.*, Carroll Cert., Exhibit B, Kessler Dep. at 265:14-23. ("Counselor, again, my standard, again, is [the FDA labeling standard of] reasonable evidence of a causal association, . . . I leave it to you . . . what causality is."). Indeed, he expressly stated that he would "leave [it] to the lawyers and the courts" whether that standard was the same as medical causation. *Id.* at 150:25-151:3. The courts have made clear it is not.

A causation opinion based on the regulatory labeling standard sheds no light on general causation, and multiple federal courts have exclude regulatory causation opinions for this reason. In *Monroe v. Novartis Pharms. Corp.*, for example, the district court precluded an FDA expert from offering causation opinions tied to the regulatory labeling standard because: "regulatory causation *is not recognized as a legitimate form of causation*." No. 1:12-cv-746, 2014 WL 12586426, at *5 (S.D. Ohio Sept. 15, 2014) (emphasis added), Carroll Cert., Exhibit K, (citing *Matthews v. Novartis Pharms. Corp.*, No. 3:12-cv-314, 2013 U.S. Dist. LEXIS 153519, at *67-68 (S.D. Ohio Sept. 20, 2013) Carroll Cert., Exhibit L.

In *Rowland v. Novartis Pharms. Corp.*, the court precluded a regulatory expert from offering "causation testimony of any kind." 9 F. Supp. 3d 553, 562

(W.D. Pa. 2014); *see also In re Mirena IUD Prod. Liab. Litig.*, 169 F. Supp. 3d 398, 476 (S.D. N.Y. 2016) (excluding opinion based on "causal association" under 21 C.F.R. § 201.57(c)(6) [labeling regulation] for failure to differentiate that standard from "general medical causation"); *Guenther v. Novartis Pharms. Corp.*, No. 6:08-cv-456-Orl-31DAB, 2013 WL 1278089, at *3 (M.D. Fla. Mar. 28, 2013) (excluding opinions "regarding any alleged 'causal association'" between drug and injury) Carroll Cert., Exhibit M.

In *In re Trasylol Prods. Liab. Litig.*, the court excluded such opinions in part because the expert could not respond to a cross-examination question asking why she was not simply offering "a back door causation opinion in the guise of talking about information available and regulatory affairs[.]" 709 F. Supp. 2d 1323, 1340 (S.D. Fla. 2010). Similarly, the court in *Georges v. Novartis Pharm. Corp.* rejected an opinion about "regulatory 'causal association'" as "confusing at best" and likely to impermissibly allow the jury to rely on the opinion in evaluating causation. No. CV 06-5207 SJO (VBKx), 2012 WL 9064768, at *10 (C.D. Cal. Nov. 2, 2012) Carroll Cert., Exhibit N.

The cases rejecting regulatory causation opinions rest on a decades-old body of law recognizing that the FDA's regulatory warning standard is precautionary and irrelevant to scientific questions of causation. The FDA itself has stated that its decisions "need not meet the standard of proof required to prevail in a private tort

action." 67 Fed. Reg. 72555, 72556 (FDA Dec. 6, 2002) (citing *Glastetter v. Novartis Pharms. Corp.*, 252 F. 3d 986, 991 (8th Cir. 2001)). And the agency has reiterated that position time and again. *See, e.g.*, Carroll Cert., Exhibit C, FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, MEDWATCH CONTINUING EDUCATION ARTICLE: THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING 2 (1996), https://www.fda.gov/downloads/Safety/MedWatch/UCM168505.pdf ("**Causality** is **not** a prerequisite for MEDWATCH reporting; **suspicion** that a medical product may be related to a serious event is sufficient reason for a health professional to submit a MEDWATCH report.") (emphases in original); Exhibit D, FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: E2E PHARMACOVIGILANCE PLANNING 12 (2005), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf ("Series of case reports . . . are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome."); *see also* discussion, *infra*, at section II(A).

In *Glastetter*, for example, the plaintiff offered as proof of general causation the FDA's determination that Parlodel was no longer shown to be safe and effective. 252 F.3d at 991; *see* 59 Fed. Reg. 43347-01, 43351 (FDA Aug. 23, 1994). The court, however, found the FDA's action not only insufficient to prove

causation, but "*irrelevant* in determining the threshold question posed in this appeal: *whether Glastetter's experts properly 'ruled in' Parlodel as a cause of [strokes]*." *Glastetter*, 252 F.3d at 991 (emphases added).

Courts across the country have ruled the same. *See, e.g.*, *In re Denture Cream Prods. Liab. Litig.*, No. 09-2051-MD, 2011 WL 9375632, at *14 (S.D. Fla. July 22, 2011) ("Plaintiffs' experts may not establish causation by reliance on the FDA Notice.") Carroll Cert., Exhibit O; *Newton v. Roche Laboratories, Inc.*, 243 F. Supp. 2d 672, 677 (W.D. Tex. 2002) (rejecting labeled warning as proof of causation under *Daubert* because "tort law requires a 'higher standard' of causation."); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 543 (W.D. Pa. 2003) (rejecting FDA action as proof of causation because FDA's mission is not to determine causation, but "to control which drugs are marketed in the United States and how they are marketed."); *see also Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1234 n. 9 (W.D. Okla. 2000), *aff'd in part and remanded*, 289 F.3d 1193 (10th Cir. 2002) (FDA's standard reflects a "'preventative perspective.'") (quoting *Mitchell v. Gencorp Inc.*, 165 F.3d 778, 783 n. 3 (10th Cir. 1999)); Federal Judicial Center, Reference Manual on Scientific Evidence 33 (2d ed. 2000) ("[R]isk assessors may pay heed to any evidence that points to a need for caution, rather than assess the likelihood that a causal relationship in a specific case is more likely than not.").

In short, Dr. Kessler's causal association opinion based on the federal regulatory labeling standard does not "fit" the issue before the Court and should be excluded from any general causation analysis.

II. DR. KESSLER'S REGULATORY CAUSATION OPINION - EVEN IF IT WERE RELEVANT TO GENERAL CAUSATION - IS NOT DERIVED FROM A RELIABLE, SCIENTIFIC METHODOLOGY.

A. Dr. Kessler's Disregard of High-Level Evidence in Favor of Case Reports Is Unscientific and Precludes Reliance on His Causal Association Opinion to Support General Causation.

Dr. Kessler ignores four of five epidemiologic studies that did not find a statistically significant causal association between olmesartan and sprue-like enteropathy. *See* Carroll Cert., Exhibit E Deposition of Daniel A. Leffler, M.D. ("Leffler Dep.") at 282:1-4, 312:7-313:10 (conceding that four of five epidemiological studies, including the double-blind, randomized controlled ROADMAP study, showed no statistically significant association). When expressly challenged at his deposition to identify evidence not supporting his opinions, Dr. Kessler still ignored the epidemiology, responding that two of 62 case reports Dr. Leffler excluded were the only "things that come to mind[.]" Carroll Cert., Exhibit B., Kessler Dep. at 168:2-169:1.

Dr. Kessler certainly is familiar with this branch of science, since he relied on epidemiological studies in unsuccessfully offering a general cause opinion for plaintiffs in the Zoloft litigation. *See In re Zoloft (Sertralinehydrochloride) Prod.*

Liab. Litig., 176 F. Supp. 3d 483, 496-97 & 496 n. 81 (E.D. Pa. 2016) (noting "Dr. Kessler does recognize the importance of [epidemiologic] evidence in establishing causation" but excluding his opinion in part because "there is no evidence that Dr. Kessler himself has reconciled the contrary studies using scientifically acceptable methodology.")

In the hierarchy of scientific evidence relevant to causation, epidemiology is at the apex. *See Norris*, 397 F.3d at 882. Dr. Leffler (on whom Dr. Kessler relies extensively) concedes as much. *See* Carroll Cert., Exhibit E, Leffler Dep. at 283:9-25 (agreeing case reports, opinion papers, and letters are the "very bottom" of the hierarchy of evidence.) Here, there is a randomized controlled trial (ROADMAP) and three observational epidemiological studies finding no causal association between olmesartan and sprue-like enteropathy, and only one observational epidemiological study reaching a contrary result. *See* Carroll Cert., Exhibit F, J. Menne et al., *Olmesartan and Intestinal Adverse Effects in the ROADMAP Study*, Mayo Clin. Proc. at 1230-1232 (December 2012); Exhibit G, R. Greywoode et al., *Olmesartan, other anti-hypertensives, and chronic diarrhea among patients undergoing endoscopic procedures; a case control study*, Mayo Clin. Proc., Sept. 2014, at 1239-1243; Exhibit H, S. Lagana et al., *Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers*, Journal of Clinical Pathology, 2015, at 29-32; Exhibit I, R. Padwal et al.,

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus, Hypertension, May 2014, at 977-983. The Manual on Scientific Evidence explains that a randomized controlled trial is the "gold standard" and "the best way to ensure that any observed difference between the two groups in outcome is likely to be the result of exposure to the drug". FJC, Reference Manual on Scientific Evidence at 555 (3d ed. 2011).

Dr. Kessler fails to explain why he ignored available epidemiologic studies. He does cite a number of sources, including FDA statements about case reports, the Bradford-Hill criteria, and various causality assessment tools, including the one used by defendants, as support for his reliance on case reports. Carroll Cert., Exhibit A, Kessler Rep. at ¶¶ 35-53. But none supports ignoring epidemiology in favor of case reports when drawing conclusions about general causation, for the reasons set out in Defendants' *Daubert* motions addressing Drs. Leffler, Lebwohl, Lagana and Hutfless, which defendants incorporate by reference and will only briefly address here. *See* Defendants' Brief in Support of Motion to Exclude Testimony of Dr. Daniel Leffler and Dr. Benjamin Lebwohl; Defendants' Brief in Support of Motion to Exclude the Testimony of Plaintiffs' Expert Susan Hutfless, Ph.D.; Defendants' Brief in Support of Motion to Exclude the Testimony of Plaintiffs' Expert Dr. Stephen Lagana. The reasons include:

The FDA's standards for evaluating case reports do not assess scientific causation, for the reasons explained in Section I, *supra*. *See* Carroll Cert., Exhibit A, Kessler Rep. at ¶¶ 41-48. The FDA itself has made this point repeatedly, stating, for example, that adverse event reports may reflect "quite subjective and imprecise" evaluation of product-relatedness, that it is established that "placebos and even no treatment can be associated with adverse events," and that unlike data from clinical trials "which are obtained under strictly controlled conditions, spontaneously reported information is uncontrolled, and therefore subject to the possible influence of a number of biases that can affect reporting."). *See* Carroll Cert., Exhibit C, FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, MEDWATCH CONTINUING EDUCATION ARTICLE: THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING 2 (1996), https://www.fda.gov/downloads/Safety/MedWatch/UCM168505.pdf; *see also* Exhibit J, FOOD AND DRUG ADMIN., CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF EPIDEMIOLOGY AND BIOSTATISTICS, DIVISION OF PHARMACOVIGILANCE AND EPIDEMIOLOGY, SURVEILLANCE AND DATA PROCESSING BRANCH, ANNUAL ADVERSE DRUG EXPERIENCE REPORT: 1996 1 (1997) (adverse event data "may not be used to calculate instances or estimates of drug risk.").

The Bradford-Hill criteria assess associations found in epidemiologic studies, and do not provide a methodology for deriving general causation opinions

from case reports. *See* Carroll Cert., Exhibit A, Kessler Rep. at ¶ 35; *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 677-80 (M.D.N.C. 2003); *see also In re: Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 925 (D.S.C. 2016).

Neither the causality assessment tools nor the clinical practice textbook Dr. Kessler cites support using case reports to assess general causation in the context of a *Daubert* hearing. *See* Carroll Cert., Exhibit A, Kessler Rep. at ¶¶ 36-42.; *see also, e.g., Glastetter v. Novartis Pharm. Corp.*, 107 F. Supp. 2d 1015, 1037 n. 21 (E.D. Mo. 2000), *aff'd* 252 F.3d 986 (8th Cir. 2001) (causality assessment scales lack objective reliability); *Soldo*, 244 F. Supp. 2d at 465, ¶ 256 (causality assessment "data are not controlled or subject to statistical evaluation and the 'assessment' is necessarily based on the self-selected and limited information provided."); *Okuda v. Wyeth*, No. 1:04-CV-80DN, 2012 WL 12337860, at *2 (D. Utah July 24, 2012) ("The causality assessments are clearly not a scientifically reliable means to determine the cause of cancer and will not be admitted for this purpose.") Carroll Cert., Exhibit P.

A reliable assessment of causation cannot ignore available epidemiology. *Norris*, 397 F.3d at 882.

B. Dr. Kessler's Process for Selecting Case Reports Is Subjective, Skewed Toward a Predetermined Result, and Almost Entirely Based on Dr. Leffler's *Ipse Dixit*.

Daubert precludes opinions grounded in "a subjective, conclusory approach that cannot reasonably be assessed for reliability." *Campbell, Jr. v. Consol. Rail Corp.*, No. 1:05-CV-1501, 2009 WL 36890, at *5 (N.D.N.Y. January 6, 2009) Carroll Cert., Exhibit Q. A reliable opinion about causation must instead be rooted in "scientific knowledge." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d Cir. 1994). And "*any* step that renders the analysis unreliable under the *Daubert factors renders the expert's testimony inadmissible.*" *Id.* at 745 (emphasis in original).

Dr. Kessler relies on 60 case reports that he and Dr. Leffler opine show "olmesartan-associated enteropathy," and include a positive rechallenge (*i.e.*, symptoms abated when the patient stopped taking the drug and returned when she restarted it). *See* Carroll Cert., Exhibit A, Kessler Rep. at § VII. His process for selecting and reviewing these reports must rest on objective criteria objectively applied—even to support an opinion about causal association. His process falls short in multiple respects. Indeed, it exemplifies why anecdotal data derived from often incomplete and ambiguous case reports merely "raise questions [but] do not answer them." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1254 (11th Cir. 2005).

1. Uncertain and subjective search terms.

Dr. Kessler cannot explain with reasonable specificity how the approximately 9,540 case reports defendants produced "were reviewed for evidence of serious rechallenge cases involving olmesartan and symptoms of olmesartan associated enteropathy." Carroll Cert., Exhibit A, Kessler Rep. at ¶ 77. He did not even conduct the search but rather gave a list of terms and date ranges to plaintiffs' counsel and then "spot-checked" the results. Carroll Cert., Exhibit B, Kessler Dep. at 175: 15-177:2. Another MDL court recently noted with disfavor Dr. Kessler's reliance on schedules prepared by legal counsel at his request: "The Court . . . cannot conclude that these schedules represent analysis by Dr. Kessler, rather than by unknown staff employed by Plaintiffs' counsel." *In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 176 F. Supp. 3d at 497 n. 82.

Dr. Kessler states the search was designed to find "serious reports with a positive rechallenge and symptoms (terms) of diarrhea, vomiting, and/or celiac disease." Carroll Cert., Exhibit A, Kessler Rep. at ¶ 77. But he did not maintain his search term list, and could not reproduce specific terms or identify specific date ranges searched. Carroll Cert., Exhibit B, Kessler Dep. at 190:19-191:6 ("I think the instructions I gave was did anything that signaled rechallenge . . . I don't recall exactly . . . I have a couple of them written down, I think, somewhere.), 191:15-17 ("[A]t some point I made a list. I don't recall exactly, I have to go back and

reconstruct that in my head."), 172:12-25 ("I have to go back and double-check. . . . It was meant to be a ten-year period.").

Opinions generated through a data selection process incapable of being replicated and evaluated for accuracy do not survive *Daubert* review. *See Zenith Elecs. Corp. v. WH-TV Broadcasting Corp.*, 395 F.3d 416, 419 (7th Cir. 2005) ("Someone else using the same data and methods must be able to replicate the result"). Dr. Kessler's inability to describe how he culled 62 reports from 9,540 except in vague and subjective terms is alone reason to exclude his opinion.

2. Failure to define "Olmesartan-Associated Enteropathy".

Dr. Kessler's "reasonable evidence of a causal association" opinion begs a key question—a causal association with what? Dr. Kessler testified that serious diarrhea and vomiting are characteristic of what he terms "olmesartan-associated enteropathy," but refused to be pinned down on the specifics of what other criteria he and Dr. Leffler relied on. *See, e.g.*, Carroll Cert., Exhibit B, Kessler Dep. at 160:16-17, 165:9-10 (olmesartan-associated enteropathy characterized by "severe gastrointestinal symptoms," or "the serious constellation of symptoms"; *see also* Carroll Cert., Exhibit E, Leffler Dep. at 18:8-19:6 (criteria of Mayo Clinic article are merely "representative," because "olmesartan enteropathy" includes "a wider spectrum of symptoms."); *see also* Exhibit B, Kessler Dep. at. at 238:19-21 ("Q.

Where did you get the term 'olmesartan-associated enteropathy'? A. I have no idea . . . I—you know, I have—I have seen it. I have seen it in different places. . . .").

Dr. Kessler rejected as "too vague" the criteria used by the Mayo Clinic authors to identify SE, and did not analyze whether any of his 60 cases would have qualified for the Mayo case series. *Id.* at 238:19-239:6, 246:15-21. His explanation does not reflect the approach of an objective scientist:

> I mean, "sprue-like enteropathy" to me is too vague because there are other things, *so I wanted to make sure that what we are talking about was an enteropathy that was associated with olmesartan, because that's what I care about, that clinical picture.*

Carroll Cert., Exhibit B, Kessler Dep. at 239:1-6 (emphasis added). When asked what criteria he supplied to Dr. Leffler, Dr. Kessler's response was similarly unilluminating: "[W]hat he saw, observed, was it consistent with a—with a defined kind of pharmacologically and phenomenologically syndrome, and, I mean, did it fit that, that pattern." *Id.* at 330:17-20. In like manner, his written instructions to Dr. Leffler identified no objective criteria, but merely asked for a determination whether "the presentation of symptoms in each of these patients after taking olmesartan is consistent with the clinical syndrome of olmesartan-associated enteropathy." *See* Carroll Cert., Exhibit B, Kessler Dep. at 200:7-19; *see also id.* at 200:20-25 (Kessler provided no further guidance to Dr. Leffler).

Dr. Kessler appears to be saying that olmesartan-associated enteropathy is characterized by symptoms that show it is olmesartan-associated enteropathy. This kind of circular reasoning is a hallmark of unreliability. *See Soldo*, 244 F. Supp. 2d at 522, ¶ 922 ("Dr. Petro's attempt to rule out AVM as an alternative cause of plaintiff's stroke by relying on the fact that she had taken Parlodel is circular and evidence of an unreliable scientific methodology."); *Jones v. Bagley*, No. C-1:01-cv-564, 2010 WL 654287, at * 54 (S.D. Ohio Feb. 19, 2012) (rejecting "circular reasoning [that] 'this is a bite wound because *eikenella* is present and *eikenella* is present because this is a bite wound.'") Carroll Cert., Exhibit R.

Because he fails to objectively define the clinical entity with which he claims olmesartan is causally associated, Dr. Kessler's methodology is too subjective to be reproducible or reviewable for reliability. *Cf. In re Denture Cream Prods. Liab. Litig.*, No. 09-2051-MD, 2011 WL 9375632, at *10 (S.D. Fla. July 22, 2011) (discounting probative value of case reports where disease lacked "a well-established clinical presentation" and reports may not have used plaintiffs' experts' definition) Carroll Cert., Exhibit O. This subjective, "I know it when I see it" approach pervades the whole of Dr. Kessler's analysis.

3. Subjective and biased review of case reports.

Dr. Kessler calls positive rechallenge "a bedrock methodology of establishing a reasonable causal association between a drug and an adverse event."

Exhibit A, Kessler Rep. at ¶ 1. It follows that the bedrock of his causal association opinion is his identification of 60 case reports reflecting positive rechallenge. But his deposition testimony reveals that his classification process depended largely on subjective judgment calls. When pressed to specify his selection process, Dr. Kessler used phrases like "clinical gestalt," "the clinical ring," and "total clinical picture." Carroll Cert., Exhibit B, Kessler Dep. at 202:12-18, 259:19. Dr. Kessler, a pediatrician by training, has never diagnosed a patient with olmesartan-associated enteropathy; nor has he published on that subject or others relevant to the medical issues in this case. *See id.* at 48:2-4, 65:25-66:4, 157:20-158:12. A methodology dependent on an individual physician's "clinical gestalt"—particularly that of a non-specialist—epitomizes the "subjective, conclusory approach that cannot reasonably be assessed for reliability." *See Campbell, Jr.*, 2009 WL 36890 at *5.

Equally emblematic of a subjective and unverifiable approach is an expert's inability to quantify how much data is necessary to support his conclusion. Dr. Kessler could not say how many purported rechallenge case reports were "enough," ultimately summarizing: "[P]eople can decide for themselves." Carroll Cert., Exhibit B, Kessler Dep. at 310:21-22; *id.* at 309:6-310:22 (refusing to specify how many case reports were sufficient to show a causal association under the FDA standard and admitting "it's not that I have a magic number"). But "'[h]ypotheses are verified by testing, not by submitting them to lay juries for a

vote.'" *Chapman v. Proctor & Gamble*, 766 F.3d 1296, 1311-12 (11th Cir. 2014) (quoting *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1367 (S.D. Fla. 2011)).

Dr. Kessler also repeatedly declined to identify objective criteria for handling various potentially confounding factors in case reports. On the contrary, his responses to hypothetical questions on this point reflect precisely the sort of data-skewing toward a predetermined result that objective criteria guard against. For example, when asked whether it would matter if the symptom that abated on dechallenge was an event other than diarrhea, vomiting, or celiac, Dr. Kessler responded: "So what mattered . . . [was] whether, as a clinician, when I read these, right, did I believe . . . that the rechallenge . . . really was a good rechallenge . . . [B]ecause when you think about it, *if there is a good rechallenge, it is—it's not confounded*." Carroll Cert., Exhibit B, Kessler Dep. at 201:6-202:5 (emphasis added). In other words, a potential confounder is *per se* irrelevant so long as Dr. Kessler—"as a clinician" (who has never diagnosed the condition at issue)—declares the case report to show a "good rechallenge." This is reminiscent of Dr. Kessler's circular definition of "olmesartan-associated enteropathy," and is equally emblematic of a subjective and unreliable methodology. *See Soldo*, 244 F. Supp. 2d at 522, ¶ 922.

Dr. Kessler's deposition testimony contains other examples of similarly biased and subjective reasoning:

- When asked whether it mattered under his positive rechallenge "criteria" if the patient was receiving treatment for the symptom during the period it abated (the dechallenge), Dr. Kessler dismissed this as a potential confounder, because it would be "highly coincidental" if anything but olmesartan caused the symptom to reappear. Carroll Cert., Exhibit B, Kessler Dep. at 203:23-204:22; *see also id.* at 205:20-206:20 (it would not matter if the symptom returned when treatment for it was discontinued, because that is "not the way these things work" and only if the patient stopped and restarted ingestion of gluten and olmesartan at the "exact same time" would he consider there to be a confounder).

- When asked if he instructed Dr. Leffler to require complete resolution of symptoms for a positive dechallenge, Dr. Kessler's response was vague and unmoored to any neutral standard: "I was looking for—well, I was looking for—no, I—what I was requiring, okay, was a—what I asked him to do was to tell me whether there was a positive rechallenge. So he got to interpret medically and use his clinical judgment, was this a positive rechallenge." Carroll Cert., Exhibit B, Kessler Dep. at 210:9-211:18.
- When asked how he would handle a case report containing ambiguous information about rechallenge, Dr. Kessler would ask Dr. Leffler to "[u]se your judgment. Do you think—use your—a rechallenge, read the—through all the data I have given you. Do you think from this clinical story, is—is this rechallenge confounded or is it not confounded." *Id.* at 212:5-11; *see also id.* at 212:12-2:13:4 (Dr. Kessler was "not that concerned" about a confounded rechallenge because Dr. Leffler said it "strains credibility" to think something other than olmesartan caused a symptom to resume).

The manner in which Dr. Kessler answered—or refused to answer—hypothetical questions testing his "positive rechallenge" selection method reveals a pattern of biased assumptions supporting a predetermined conclusion. And the subjective nature of Dr. Kessler's review appears to have led him to put his thumb on the scale for plaintiffs in other respects as well. For instance, he applied a double-standard when assessing the credibility of patient-reported symptoms. A report in which the patient stated her symptoms came and went depending on whether she was taking olmesartan conclusively established a causal association, making other factors not apparent from the report—diet, other medications—"pretty much irrelevant." Carroll Cert., Exhibit B, Kessler Dep. at 255:6-12, 257:23-258:24, 259:21-23. Yet Dr. Kessler also included a report reflecting the patient's belief that olmesartan did *not* cause her symptoms, and when asked why, offered an explanation bereft of objective reasoning:

> There was no—I mean, why would—there was no information that Benicar would cause that, so why would the patient think that. And, two, there is a lot of misdiagnosis on celiac. Every—I mean, you and I, we—clinically we know that there is a lot of misdiagnosis, so there is a lot of misinformation.

Id. at 266:25-267:14. In like manner, he refused to concede that the Mayo Clinic authors treating live patients had better medical history data than he— because patients "are not as good historians." *Id.* at 250:22-251:6.

Assigning weight to evidence depending on whether it supports one's preferred hypothesis signals a subjective, outcome-oriented, and unreliable approach. *See In re TMI Litig.*, 193 F.3d at 704 (affirming exclusion of expert who manipulated a subjective scoring system to tilt the results in the plaintiffs' favor). So, too, does resorting to advocacy, as Dr. Kessler did. Carroll Cert., Exhibit B, Kessler Dep. at 267:20-268:8 (sidestepping question about the patient who did not think her symptoms were caused by olmesartan and lecturing defense counsel: "[T]the problem I have with your client's conduct here was you don't explain away things and look for excuses. That's what happened here."). Advocacy will not substitute for a reliable methodology. *See In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.*, 593 F. Supp. 2d 549, 564 (S.D. N.Y. 2008) (expert should "leave the advocacy to the lawyers.").

The Third Circuit explained in *In re TMI Litig.* that "it is impossible to test a hypothesis generated by a subjective methodology because the only person capable of testing or falsifying the hypothesis is the creator of the methodology." 193 F.3d at 703 n. 144; *see also Elcock v. Kmart Corp.*, 233 F.3d 734, 747 (3d Cir. 2000) ("[B]ecause Copemann never explained his method in rigorous detail, it would have been nearly impossible for Kmart's experts to repeat Copemann's apparently subjective methods[.]"). Dr. Kessler's process for compiling his list of 60 cases

report lacks objective standards permitting meaningful review. The opinions he derived from it are, accordingly, inadmissible.

4. Uncritical reliance on Dr. Leffler's *ipse dixit*.

Experts may rely on the opinions of other experts under Federal Rule of Evidence 703. But they may not "simply 'parrot' those experts' ideas. *Leese v. Lockheed Martin Corp.*, 6 F. Supp. 3d 546, 553 (D. N.J. 2014). In *In re TMI Litig.*, for example, the Third Circuit affirmed the district court's exclusion of an expert based on his "failure to assess the validity of the opinions of the experts he relied upon together with his unblinking reliance on those experts' opinions[.]" 193 F.3d at 716. These factors signaled an unreliable methodology "not calculated to produce reliable results." *Id.* at 716.

Even less reliable is complete trust in another expert's say-so. *Cf. General Elec. v. Joiner*, 522 U.S. 136, 146 (1997) (a court is not required "to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."). At first, Dr. Kessler testified that he himself is qualified to diagnose "olmesartan-associated enteropathy," and claimed to have confirmed Dr. Leffler's findings after careful review. Carroll Cert., Exhibit A, Kessler Rep. at ¶ 79; Carroll Cert., Exhibit B, Kessler Dep. at 201:13-23 (testifying that he "read these forms very carefully," used a "totality of clinical judgment," and determined "whether that rechallenge really was a good rechallenge."). But he quickly backed off that testimony as the

deposition progressed, repeatedly deferring to Dr. Leffler when unsure how various questions raised by case reports should be handled: For instance, Dr. Kessler counted reports where the time from first ingestion of olmesartan until initial onset of symptoms ranged from one month to five years. Carroll Cert., Exhibit A, Kessler Rep. at p. 31 (## 34, 40, 41). Yet when asked how this wide span in time periods factored into his analysis, Dr. Kessler deferred to Dr. Leffler. Carroll Cert., Exhibit B, Kessler Dep. at 294:17-295:16 ("I think, if I'm correct, Leffler did raise that issue and took that into account.").

This pattern of wholesale reliance on Dr. Leffler continued in Dr. Kessler's deposition. *See* discussion, *supra*, at subsection (3); *see also* Carroll Cert., Exhibit B, Kessler Dep. 192:9-21 (when asked whether time to improvement of symptoms was used in selection process, Dr. Kessler answered "it was certainly one of the criteria that—I believe Dr. Leffler, that's the kind of clinical judgment that I wanted."). In fact, Dr. Kessler was unable to articulate with any specificity how he would rule a report in or out if Dr. Leffler was unsure. *Id.*at 215:9-15 ("Q. And would you have said to Dr. Leffler, if he had asked you, 'Don't count that one'? A. I would say 'Tell me whether you think it's a positive rechallenge or a . . . true positive rechallenge,' which would mean, in essence, the—the drug was the causative agent here, was—was linked."). In sum, regardless of whether Dr. Leffler used reliable criteria to rule case reports in or out (he did not, as more fully

explained in defendants' motion challenging his opinions), it is fair to say that if Dr. Leffler called it "olmesartan-associated enteropathy," that was good enough for Dr. Kessler:

> Q. . . . If it were unclear which of the events reported here got worse upon restarting olmesartan, would the report count or not count for your opinion?
>
> A. So this—so this would only count if . . . Dr. Leffler had concluded that it was consistent with olmesartan-associated enteropathy—I think he uses the term "olmesartan-associated enteropathy"—and not consistent with something else. That's the only way it would count.
>
> Carroll Cert., Exhibit B, Kessler Dep. at 243:25-14 (objection omitted).
>
> Q. . . . Going into the future, she says she is continuing to have episodes, but she has gone off Benicar, so future, after this report. Would that be irrelevant to you, that information?
>
> A. . . I would have expected, if those were the facts, that Dr. Leffler would look at those facts and say whether that pattern is consistent with olmesartan-induced enteropathy. . . . I don't know what he would have said.

Id. at 264:3-265:8 (objection omitted).

> Q. . . . And so 60 that you identified or Dr. Leffler identified as supporting or being consistent with what you call olmesartan-associated enteropathy?
>
> A. Yes . . . because I really don't care what the name is. What I care was serious GI that was—that had a positive rechallenge where a—that a seasoned gastroenterologist looked at and said it was

> consistent with a picture of the syndrome induced by olmesartan. That's how I got to the 60.
>
> Q. And would it be irrelevant to you, in deciding whether a report was going to be one of the 60, that the patient did not believe that Benicar was the cause of her events?
>
> A. So that—again, I mean, *I didn't use independent judgment on that. Leffler made that call*, but let me just tell you—but I am happy to tell you my opinion on this.

Id. at 266:12-267:7 (emphasis added).

By leaving it to Dr. Leffler to decide if a case report was in or out—and then deferring to him when asked to explain methodology—Dr. Kessler demonstrates the kind of "unblinking reliance" warranting exclusion. *In re TMI Litig.*, 193 F.3d at 713-716.

CONCLUSION

Because Dr. Kessler's regulatory causation association opinion does not fit the general causation before the Court, it should be excluded from any such analysis. Even if permitted to air, it should be excluded because it is not the product of a reliable methodology.

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